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Plasma Free Platinum Pharmacokinetics in Patients Treated with High Dose Carboplatin

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Abstract—*Plasma free platinum* (< 50,000 *mol. wt*) *pharmacokinetics have been studied in eight patients treated with high-dose* (800–1600 mg/m^2) *carboplatin as a* 1 h *infusion with moderate hydration. Following the infusion, levels decayed biphasically with half-lives* ($\bar{x} \pm S.D.$) *of* 83 ± 15 min *and* 6.1 ± 2.8 h. *The plasma free platinum area under the concentration vs. time curve* (*AUC*) *at* 1600 mg/m^2 *in five patients was* 23 ± 2 mg *carboplatin*/ml.min. *Comparison with data at conventional doses* (≤ 500 mg/m^2) *gave no indication of non-linear kinetics. Total body clearance of free platinum was found to correlate with glomerular filtration rate* (r = 0.769, P = 0.03), *and haematological toxicity, white cell nadir and duration of thrombocytopenia, correlated with plasma free platinum AUC* (r = 0.784, P = 0.02 *and* r = 0.885, P = 0.01, *respectively*). *Persistence of platinum was demonstrated in tissues removed at autopsy from a patient who had received carboplatin* 14 *days earlier. Highest platinum levels were found in the liver, kidney, skin and small cell lung tumour.*

INTRODUCTION

CARBOPLATIN (*cis*-diammine-1,1-cyclobutanedicarboxylate platinum II, Fig. 1) is an analogue of cisplatin which is currently undergoing widespread clinical evaluation. Unlike cisplatin, nephrotoxicity, ototoxicity and neurotoxicity are not problematic following carboplatin at doses of 400–600 mg/m^2 administered every 4–6 weeks given over 1 or 24 h on one or over 5 days. Furthermore, nausea and vomiting are less pronounced after carboplatin. Myelosuppression in the form of thrombocytopenia is the dose-limiting toxicity most frequently reported with carboplatin [1–9].

Early results concerning the therapeutic activity of carboplatin indicate that the compound has equivalent efficacy to cisplatin in ovarian cancer [10] and that it is also active in small cell lung cancer [11], testicular cancer [12], head and neck cancer [13], cervical cancer and certain childhood malignancies [14] and abstracts reviewed in [8, 9].

In the preceeding paper [15] the activity and toxicity of high-dose carboplatin (800–1600 mg/m^2) in the treatment of lung cancer has been evaluated. The results confirm that carboplatin is an active agent against small cell lung cancer and that severe and prolonged thrombocytopenia and leucopenia are the major toxicities encountered. In addition, mild nephrotoxicity and ototoxicity were observed, as were alopecia, diarrhoea and symptoms of CNS toxicity.

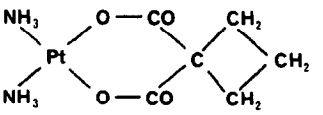

Fig. 1. The structure of carboplatin.

In connection with the clinical evaluation, investigations were performed to characterize the pharmacokinetics of plasma free platinum following carboplatin administration at doses of 800–1600 mg/m^2. Studies focussed on plasma free platinum, rather than total platinum, as the former species is the active component. Protein bound platinum is not cytotoxic [16, 17]. The pharmacokinetics of carboplatin at high doses were investigated in order to establish three points: (a) their relationship to carboplatin kinetics at conventional doses (< 600 mg/m^2) given without hydration, (b) their relationship to carboplatin-induced toxicity and (c) the time point at which bone marrow transplantation might be performed in a future study without

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risk to the transplant from residual active drug.

The pharmacokinetics of carboplatin in man have been studied following a variety of schedules and over a range of doses (20–500 mg/m^2) [2, 4, 7, 18, 19]. In comparison to cisplatin, carboplatin is an unreactive complex both *in vitro* and *in vivo*, presumably as a result of the bidentate nature of the cyclobutane dicarboxylate ligand which holds the platinum in a stable six-membered ring. Thus carboplatin reacts slowly with plasma proteins *in vitro* with a half-life of approx. 30 h (37°C) [19–21], substantially longer than that of cisplatin (approx. 2 h) [16, 22]. Similarly, *in vivo*, the plasma free platinum half-life following carboplatin (1.5–3 h) [2, 4, 7, 19] is longer than that observed after cisplatin (0.3–1.3 h) (papers cited in [19]). The use of specific HPLC assays have shown that plasma free platinum exists solely in the form of intact carboplatin ([19], and W. Van der Wijgh, personal communication). Urinary excretion is the major route of platinum clearance following carboplatin with over 50% of the administered dose present in the urine at 24 h in patients without severely impaired renal function (GFR > 60 ml/min) [4, 7, 18, 19]. Two independent studies have shown that the total body or renal clearances of plasma free platinum following carboplatin correlate with pre-treatment glomerular filtration rate (GFR) and that the slope of the regression line does not differ significantly from unity [18, 19]. Thus glomerular filtration is implicated as the sole mechanism of carboplatin renal elimination. This relationship has important therapeutic consequences in that, for a given dose, the pre-treatment renal function status of a patient is the major determinant of exposure to free platinum, i.e. active drug. Formulae have been derived which predict the dose required to achieve a given plasma free platinum area under the plasma concentration vs. time curve (AUC) regardless of the patient's surface area [18, 23]. Furthermore, the observation that thrombocytopenia correlates with plasma free platinum AUC [18] has allowed the development of an equation which accurately predicts the dose required for a given degree of thrombocytopenia [24]. Thus carboplatin represents a further example of the importance of pharmacokinetic determinants of drug toxicity. In the present study, therefore, attempts have been made to correlate both pretreatment renal function and haematological toxicity with plasma free platinum pharmacokinetics.

METHODS

Patient treatment

The patients studied were those involved in the clinical trial of high dose carboplatin described in the preceeding paper [15]. Pre-treatment renal function, carboplatin doses and drug-induced haematological toxicity are given in Table 1. GFR was determined by the technique of [^{51}Cr]EDTA clearance [25]. Carboplatin was infused i.v. over 1 h in 500 ml 5% dextrose. Moderate hydration was given, i.e. 1 l 0.15 M NaCl prior to carboplatin over 8 h and 3 l 0.15 M NaCl over the 24 h after administration, but diuretics were not used. Antiemetics (lorazepam 1 mg, metoclopramide 10 mg, dexamethazone 8 mg) were given i.v. just prior to carboplatin administration and at 6 and 18 h afterwards. All phamacokinetic studies were performed during the first course of therapy.

An indwelling i.v. cannula was placed in the arm opposite to that receiving carboplatin and patency maintained with heparin in saline. Prior to carboplatin administration, midway through the infusion, at the end of the infusion and 0.25, 0.5, 1, 1.5, 2, 4, 6, 9, 12, 18 and 24 h thereafter, 5 ml blood samples were collected into heparinized tubes and plasma prepared immediately (2000 ***g***, 15 min, room temperature). As soon as plasma was prepared 1 ml was removed and placed in an Amicon Centrifree micropartition unit (Amicon Ltd., StoneHouse, Glos., U.K.). Plasma ultrafiltrates were prepared by centrifugation at 2000 ***g*** for 15 min at room temperature and stored at −20°C until analysed.

The carboplatin was used in these studies was a gift from Bristol-Myers International Corp. (Brussels, Belgium).

During the course of this study, one patient (SS) who had received 1600 mg/m^2 14 days earlier died as a result of drug-induced bone marrow aplasia and septicaemia. Tissue samples were removed at autopsy for platinum determinations.

Platinum analyses

Platinum was determined on an Instrumentation Laboratory atomic absorption spectrophotometer (model 457) in the flameless mode (IL Ltd., Warrington, U.K.). Aliquots (10–50 μl) of plasma, plasma ultrafiltrate or blood were diluted in 2.5 ml 0.1 M HCl and analysed directly. Tissues (about 200 mg), however, required solubilization in hyamine hydroxide (0.5–1.0 ml) prior to platinum analyses, as described previously [26].

Pharmacokinetic analyses

Following the end of the infusion a bi-exponential equation of the form

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C is the concentration at time t and A, B and α, β are the concentration and rate constants, respectively, was fitted to the plasma free platinum levels using a computerized non-linear least squares technique [26]. A weighting of $1/(\hat{y}+yi)^2$ was used

Table 1. Renal function and haematological toxicity for patients treated with high dose carboplatin (first course)

Patient	Pre-treatment GFR(ml/min)	Dose (mg/m²)	Dose (total mg)	Haematological toxicity nadir % pre-treatment WBC	Platelets
MC	89	800	(1440)	20	5
EL	69	1200	(2100)	7	7
RW	116	1200	(2100)	11	5
JM	87	1600	(2900)	10	4
GS	87	1600	(2300)	4	2
SS	100	1600	(2550)	2	6
RS	109	1600	(2700)	6	5
RE	100	1600	(2800)	4	3

on all occasions [28, 97]. The resultant equation was corrected for the infusion period [30] and then used to calculate the α and β phase half-lives and volumes of distribution employing standard equations [31]. The AUC was calculated by the trapezoidal rule and also by the equation:

$$\text{AUC} = \frac{A}{\alpha} + \frac{B}{\beta}.$$

The total body clearance was calculated as:

$$\text{Clearance} = \frac{\text{Dose (total mg)}}{\text{AUC}}.$$

Correlations were investigated using linear regression analysis. Mass units refer to carboplatin (mol. wt 371) and not elemental platinum with the exception of Table 4 where μg platinum are given.

RESULTS

Plasma platinum pharmacokinetics have been investigated in eight patients following the administration of high dose i.v. carboplatin; one at 800 mg/m², two at 1200 mg/m² and five at 1600 mg/m². Figure 2 shows a representative plasma concentration plot for plasma total and free (< 50,000 mol. wt) platinum for a patient who received 1600 mg/m². Peak plasma total and free platinum levels were observed at the end of the infusion, decaying exponentially thereafter. As previously observed at lower doses [19], up until approx. 4 h after the end of the infusion, essentially all of the plasma platinum was in the free form. Thereafter, plasma free platinum was cleared more rapidly such that at 24 h the majority of the plasma platinum was in the bound form. However, as plasma protein bound platinum is not cytotoxic [16, 17] pharmacokinetic analyses were restricted to the plasma free platinum levels.

Table 2 gives the pharmacokinetic parameters derived from the bi- or in two patients, mono-

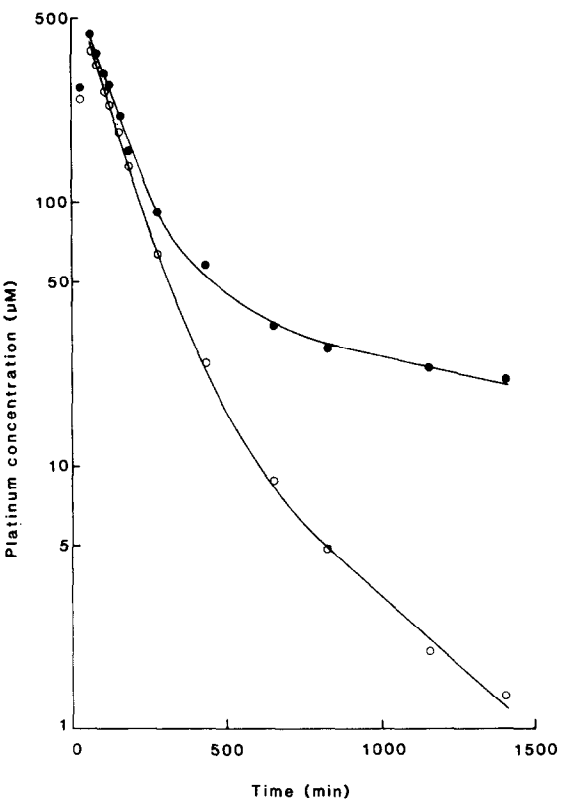

Fig. 2. Plasma levels of total (●) and free (○) platinum in a patient following 1600 mg/m² carboplatin. Lines are the computer generated fit.

exponential equation fitted to the plasma free platinum levels in each of the eight patients. The plasma free platinum AUC values are shown in Table 3, where two sets of observed values are given, namely, those derived by the model independent trapezoidal rule and those obtained by the computer fit of abi- or mono-exponential equation. The close correlation of these two sets of data ($r = 0.987$, $P = 0.000005$) supports the application of the equations used. Also given in Table 3 are the plasma free platinum total body clearance values calculated using the trapezoidal AUC. In previous studies a significant correlation has been observed between pre-treatment GFR and plasma free platinum clear-

Table 2. Plasma free platinum half-lives and volumes of distribution following high-dose carboplatin

Patient	Dose (mg/m²)	$t^{\alpha}_{1/2}$ (min)	$t^{\beta}_{1/2}$ (h)	V^{1} (l)	V_{ss} (l)
MC	800	75	—	14.5	—
EL	1200	95	4.6	12.1	14.0
RW	1200	107	—	27.5	—
JM	1600	75	6.1	15.4	21.3
GS	1600	89	11.6	13.2	19.2
SS	1600	73	5.0	12.0	15.8
RS	1600	88	5.5	20.6	27.3
RE	1600	58	4.0	14.7	22.0
$\bar{x}$ ± S.D.		83 ± 15	6.1 ± 2.8	16.2 ± 5.3	20 ± 4.8

ance [18, 19]. As shown in Fig. 3 in the patients receiving high-dose carboplatin such a correlation, albeit weak, was also found.

At conventional doses of carboplatin (≤ 500 mg/m²) a correlation has been demonstrated between the plasma free platinum AUC and carboplatin induced thrombocytopenia, expressed as the percent change in the platelet count [18]. In the present study the doses of carboplatin used resulted in such profound thrombocytopenia that differences between patients in terms of platelet nadir were difficult to discern (Table 1). However, the duration of thrombocytopenia was found to vary between patients and this parameter of haematological toxicity did correlate with the plasma free platinum AUC, i.e.

Days platelet count < 100,000/μl
$= 0.37 \times AUC + 3.7$

$r = 0.803$, $P = 0.03$

Days platelet count < 50,000/μl
$= 0.46 \times AUC - 2.1$

$r = 0.885$, $P = 0.01$.

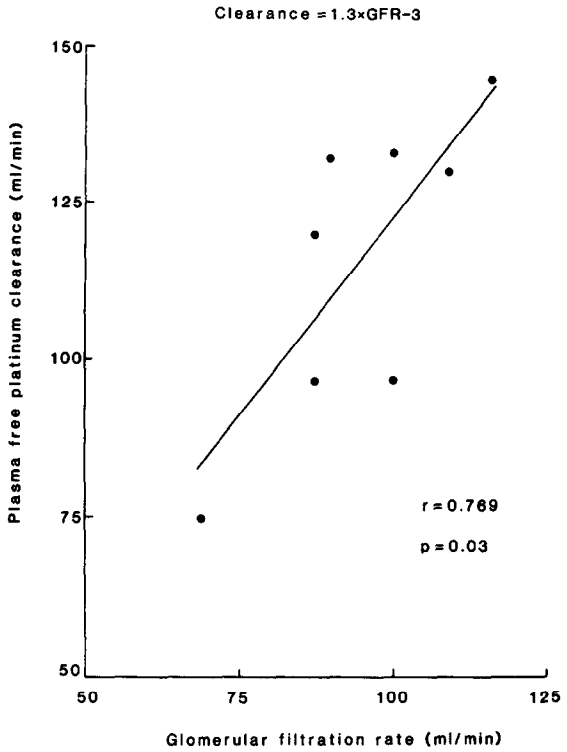

Fig. 3. Correlation of plasma free platinum total body clearance and pretreatment GFR in patients treated with high-dose carboplatin.

For both correlations the trapezoidal AUC was used.

In the current study, because of the high carboplatin doses employed, leucopenia was a more pronounced toxicity than has been observed following conventional doses. This allowed the relationship between the plasma free platinum AUC and leucopenia to be studied and, as shown in Fig. 4, a weak correlation between the AUC and white blood cell nadir was in fact observed.

Tissue distribution of platinum was determined in one patient who died 14 days after receiving carboplatin. Most tissues had a platinum level which was greater than that found in plasma (Table

Table 3. Plasma free platinum AUC and total body clearance followng high-dose carboplatin

Patient	Dose (mg/m²)	Plasma free platinum AUC (mg/ml.min)* Trapezoidal	Computer fit	Plasma free platinum Total body clearance† (ml/min)
MC	800	10.9	10.8	132
EL	1200	28.0	26.1	75
RW	1200	14.3	11.7	147
JM	1600	24.1	23.4	120
GS	1600	23.8	24.0	97
SS	1600	26.3	25.4	97
RS	1600	20.7	19.4	130
RE	1600	21.0	20.7	133

*mg refers to mg carboplatin.
†Calculated using the trapezoidal AUC.

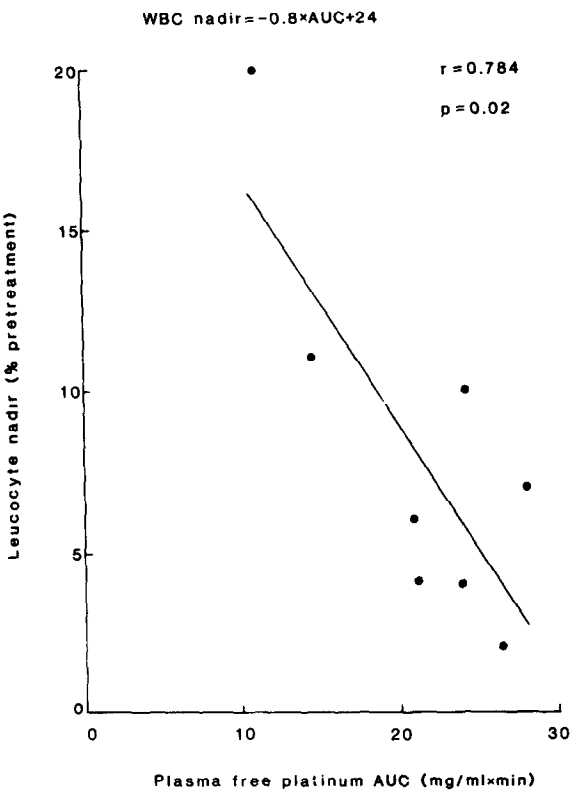

Fig. 4. Correlation of carboplatin-induced leucopenia and plasma free-platinum AUC following high-dose carboplatin.

4). Only the fat, cerebrum and cerebellum had lower concentrations. Highest concentrations were found in the liver, kidney, skin and both the primary and secondary tumour. Interestingly, platinum levels were greater in the tumour than in the corresponding normal tissue.

DISCUSSION

High-dose studies are an important component of the evaluation of a new antitumour agent in that they allow the full extent and spectrum of activity of a drug to be defined. In the preceeding paper it has been demonstrated that up to 1600 mg/m^2 carboplatin can be safely administered to the majority of patients and that this therapy gives responses in small cell lung cancer, albeit of short duration [15].

Pharmacokinetic studies are an important component of initial high-dose trials in that they may detect and therefore allow compensation for non-linear pharmacokinetics. In addition, for those drugs which require bone marrow transplantation following high-dose therapy, drug level monitoring is essential to ensure that cytotoxic drug concentrations are no longer present at the time of transplantation. Although bone marrow transplantation was not in fact used in the present study, if it had been required it could have been performed safely at 24 h or even earlier.

With high dose carboplatin no evidence of non-linear kinetics has been observed. In our previous studies [19] in patients treated at 400 mg/m^2 the plasma free platinum $t_{\frac{1}{2}}^{\alpha}$, $t_{\frac{1}{2}}^{\beta}$ and AUC values ($\bar{x} \pm$ S.D.) were 88 ± 5 min, 5.9 ± 0.8 h and 4.9 ± 1.0 mg/ml.min, respectively. Comparison of these data with those in the present study (Tables 2 and 3) indicate that the α and β phase half-lives were the same and that the AUC at 1600 mg/m^2 was appropriately related. Furthermore, following high dose carboplatin the total body clearance of

Table 4. Tissue distribution of platinum in patient SS treated with 1600 mg/m^2 *carboplatin (tissues removed following death on day* 14)

Tissue/fluid	Concentration (μg* Pt/ml or g)	Tissue : plasma ratio
Fat	0.24	0.53
Cerebrum	0.27	0.60
Cerebellum	0.35	0.78
Plasma	0.45	1.00
Blood	0.48	1.07
Skeletal muscle	0.49	1.09
Femoral bone marrow	0.90	2.00
Spleen	0.90	2.00
Large intestine	1.29	2.87
Small intestine	1.37	3.04
Ovary	1.77	3.93
Heart	1.85	4.11
Stomach	2.54	5.64
Lung	2.67	5.93
Peripheral nerve	2.75	6.11
Liver	4.16	9.24
Kidney	4.17	9.27
Lung, primary tumour	4.42	9.82
Liver, secondary tumour	4.81	10.7
Skin	5.74	12.8

*μg elemental platinum.

plasma free platinum correlated with pre-treatment GFR (Fig. 3), which again agrees with data at conventional doses [18, 19]. Thus not only is there no evidence for non-linear kinetics but also the hydration protocol employed did not affect carboplatin pharmacokinetics. The fact that GFR remains a major determinant of carboplatin whole body clearance suggests that renal excretion remains an important route of carboplatin elimination. In the present study the ratio of the plasma free platinum total body clearance to GFR was, as at conventional doses, close to unity (Fig. 3) thereby implicating glomerular filtration as the mechanism of renal clearance.

Although pharmacokinetic studies are inherently valuable as an aid to understanding the fate of drugs *in vivo* they are only of practical value when a link can be established with activity or toxicity. Carboplatin provides one of the few examples in cancer chemotherapy where this is the case. In a retrospective analysis, Egorin *et al.* [18] have shown that total body clearance correlates with pre-treatment GFR and that the plasma free platinum AUC correlates with thrombocytopenia, expressed as the % change in platelet count at the nadir. These two observations led to the derivation of an equation which predicted thrombocytopenia for a given dose and pre-treatment GFR. Prospective validation of this equation has shown that it is indeed highly predictive [24]. The severe thrombocytopenia observed in the present study precluded any meaningful study of the correlation of plasma free platinum AUC and platelet nadir, however, weak correlations were found between AUC and the duration of thrombocytopenia. Also a weak correlation between plasma free platinum AUC and white blood cell nadir was observed (Fig. 4). These data provide further evidence that free platinum exposure is the major determinant of carboplatin haematological toxicity.

Though it has yet to be proven, plasma free platinum AUC should also be a major determinant of carboplatin antitumour activity. Given that this is the case it is more logical to define high dose carboplatin in terms of plasma free platinum AUC with the dose required to achieve it calculated on the basis of the individual patient's renal function. From the data in the present and preceeding papers it is concluded that 20 mg/ml.min represents a 'high' carboplatin AUC which will yield platelet and white cell nadirs of approx. 5% of the pre-treatment values. In comparison, conventional doses of carboplatin give plasma free platinum AUC values of 5–7 mg/ml.min [2, 4, 7, 18, 19].

The distribution of platinum in a patient who died of septicaemia indicated that the small cell lung tumour had a high level of platinum. This may relate to responses observed with carboplatin in small cell lung cancer. In general, however, tissue distribution of carboplatin was qualitatively similar to that reported for cisplatin [32].

In conclusion, this study of the pharmacokinetics of high-dose carboplatin has shown that there is no evidence for non-linear pharmacokinetics up to doses of 1600 mg/m^2. Pre-treatment glomerular filtration rate remains a major determinant of the plasma free platinum AUC suggesting that even at these high doses, given with moderate hydration, renal elimination via glomerular filtration is a major route of carboplatin clearance. Haematological toxicity, expressed as duration of thrombocytopenia or leucocyte nadir, correlates with plasma free platinum AUC. Thus this study provides an additional example of the importance of pharmacokinetics as a determinant of drug toxicity.

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